JAK efficacy in Crohn's disease

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Abstract: Inhibition of Janus kinases in Crohn's disease (CD) patients has shown conflicting results in clinical trials. Tofacitinib, a pan-JAK inhibitor showed efficacy in ulcerative colitis (UC) and has been approved for the treatment of patients with moderate to severe UC. In contrast, studies in patients suffering from CD were disappointing and the primary endpoint of clinical remission could not be met in the respective phase II induction and maintenance trials. Subsequently, the clinical development of tofacitinib was discontinued in CD. In contrast, efficacy of filgotinib, a selective JAK1 inhibitor, in CD patients was demonstrated in the randomized, double-blinded, placebo-controlled phase II FITZROY study. Upadacitinib also showed promising results in a phase II trial in moderate to severe CD. Subsequently phase III programs in CD have been initiated for both substances, which are still ongoing. Several newer molecules of this class of orally administrated immunosuppressants are tested in clinical programs. The concern of side effects of systemic JAK inhibition is addressed by either exclusively intestinal action or higher selectivity (Tyk2 inhibitors). In general, JAK inhibitors constitute a new promising class of drugs for the treatment of CD.

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ABSTRACT

Inhibition of Janus kinases in Crohn's disease (CD) patients has shown conflicting results in clinical trials. Tofacitinib, a pan-JAK inhibitor showed efficacy in ulcerative colitis (UC) and has been approved for the treatment of patients with moderate to severe UC. In contrast, studies in patients suffering from CD were disappointing and the primary endpoint of clinical remission could not be met in the respective phase II induction and maintenance trials. Subsequently, the clinical development of tofacitinib was discontinued in CD. In contrast, efficacy of filgotinib, a selective JAK1 inhibitor, in CD patients was demonstrated in the randomized, double-blinded, placebo-controlled phase II FITZROY study. Upadacitinib also showed promising results in a phase II trial in moderate to severe CD. Subsequently phase III programs in CD have been initiated for both substances, which are still ongoing. Several newer molecules of this class of orally administrated immunosuppressants are tested in clinical programs. The concern of side effects of systemic JAK inhibition is addressed by either exclusively intestinal action or higher selectivity (Tyk2 inhibitors). In general, JAK inhibitors constitute a new promising class of drugs for the treatment of CD.

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INTRODUCTION

Many treatment strategies for patients with Crohn's disease (CD) and ulcerative colitis (UC) are similar despite the fact that both disease have different characteristics and most likely also different pathophysiology. Steroids, thiopurines (for maintenance of remission), anti-TNF antibodies, anti-aplha4beta7-integrin antibodies and anti-IL-23 antibodies have shown clinical efficacy in both subtypes of inflammatory bowel diseases (IBD) [1]. However, a significant number of patients still is insufficiently treated, surgery is frequent in CD and 10-15% of patients with UC still undergo colectomy.

Subsequently, Janus kinase (JAK) inhibitors were considered for clinical trials in both CD and UC and clinical trials programs for different compounds from this substance class have been established for both IBD entities [2-4]. Tofacitinib, a pan-JAK inhibitor, in the meantime has been approved for the treatment of patients with moderate to severe UC [5-11]. Reports on the clinical testing of three JAK inhibitors in patients with moderate-to-severe CD have been published: tofacitinib (pan-JAK inhibitor) [10], filgotinib (JAK1 inhibitor) [12] and upadacitinib (JAK1 inhibitor) [12].

Why did the inhibition of Janus kinases appear to be a promising new treatment strategy in IBD? Janus kinases phosphorylate activated cytokine receptors and are necessary for their signal transduction [13,14]. They are located intracellularly and belong to the large family of tyrosine kinases, enzymes that bind a phosphate group to the amino acid tyrosine (tyrosine phosphorylation) [2,15]. Subsequently, these molecules are involved in the transduction of cytokine-transmitted signals from the cell surface to the cell nucleus to modify gene expression [2,15]. Cytokines bind to their specific receptors on the surface of the target cells (e.g. lymphocytes or macrophages). After binding of the cytokines such as interleukin 6 (IL-6) or IL-2 and IL12 and IL-23 to their receptors the conformation of the receptor is changed and JAKs are activated to phosphorylate the receptor. This phosphorylation of the respective receptors by the tyrosine kinases of the JAK family allows members of the "signal transducer and activator of transcription" (STAT) protein family to bind to the receptor. They also become phosphorylated and subsequently form dimers, which then dissociate from the receptor and move into the nucleus where they change the transcription of genes [2,15].

Many cytokine receptors rely on the JAK family proteins to transmit the signals after binding of a specific cytokine molecule. In contrast, this is not the case for example for TNF receptors: TNF receptors require other proteins that get bound to them to initiate intracellular signal transduction such as “Tumor necrosis factor receptor type 1-associated DEATH domain protein” (TRADD), “TNF receptor associated factors” (TRAFs), “Receptor-interacting protein (RIP) kinases” and “Fas-associated protein with death domain” (FADD) [16-18]. Nevertheless, there is a connection between TNF and the JAK/STAT pathways: After binding of TNF to its receptor STAT proteins (that are involved in JAK induced signal transduction) are up-regulated. TNF action thereby can amplify the signal transduction of JAK dependent receptors indicating that these pathways are not completely independent but influence each other.

Receptors that use JAK family members, however, are not only mediating pro-inflammatory signals. Among the cell surface receptors that depend on JAK signaling are also the erythropoietin receptor [19] and “Granulocyte-macrophage colony-stimulating factor” (GM-CSF) [20-22] as well as “Granulocyte colony-stimulating factor” (G-CSF) [23]. This explains why JAK inhibitors can be applied in myeloproliferative disorders. It also explains some side effects seen with certain compounds such as anemia (blockade of erythropoietin signaling).

Four different proteins belong to the JAK family of tyrosine kinases: JAK1, JAK2, JAK3 and “tyrosine-protein kinase 2” (TYK2) [2]. In different combinations, usually two of these protein family members are associated with a certain receptor type [2].

JAK inhibitors are under development for a variety of disease besides IBD, such as the treatment of rheumatoid arthritis, psoriasis, polycythemia vera, alopecia, thrombocythemia, myelofibrosis and vitiligo. Different compounds have different specificities for different JAKs or TYK. There is an ongoing discussion which profile of JAK inhibition would be optimal for which specific disease. The first approved JAK inhibitor (by FDA in 2011) was ruxolitinib (trade names Jakafi/Jakavi) against JAK1/JAK2 for psoriasis, myelofibrosis and rheumatoid arthritis [24-26]. Tofacitinib (trade names Xeljanz/Jakvinus), a pan-JAK inhibitor, was first approved in November 2012 initially in rheumatoid arthritis in patients who had an inadequate response or intolerance to methotrexate [27-31]. Peficitinib (ASP015K, JNJ-54781532; trade name Smyraf) was approved for the treatment of rheumatoid arthritis in Japan in 2019 [32].

Fedratinib (SAR302503; trade name Inrebic) was approved the FDA in August 2019 for treatment of myelofibrosis and essential thrombocythemia [33]. Upadacitinib (trade name Rinvoq; ABT-494) targeting mainly JAK1 also was approved by the FDA for the treatment of rheumatoid arthritis in August 2019 [34-38].

Filgotinib (G-146034, GLPG-0634) also is relatively specific for JAK1. In spring 2019, Gilead and Galapagos announced that the Phase 3 FINCH 1 and FINCH 3 trials in rheumatoid arthritis patients met the primary and key secondary endpoints [39]. Earlier, in 2018, it was reported that the TORTUGA Phase 2 trial of filgotinib in ankylosing spondylitis met the primary endpoint [40] and well as the EQUATOR Phase 2 trial of filgotinib in psoriatic arthritis [41,42].

Further JAK inhibitors in clinical development are Cerdulatinib (PRT062070) for hematological malignancies [43,44], Gandotinib (LY-2784544) for myeloproliferative neoplasms [45], Lestaurtinib (CEP-701) for acute myeloid leukemia [46,47], Momelotinib (GS-0387, CYT-387) for myeloproliferative disorders [48,49], Pacritinib (SB1518) for relapsed lymphoma and advanced myeloid malignancies [50,51] and PF-04965842 for atopic dermatitis and moderate to severe psoriasis [52].

METHODS

For this review on the efficacy of JAK inhibitors in CD, PubMed, Embase and CENTRAL were systematically searched to October 1, 2019. Randomised placebo-controlled trials (RCTs) of JAK inhibitors in adult patients with CD were eligible. Additional information was retrieved from the Trials.gov database. MEDLINE was searched via PubMed, EMBASE via Ovid and The Cochrane Central Register of Controlled Trials (CENTRAL).

Furthermore, the reference lists of included studies and systematic reviews from the last five years on JAK therapy for management of inflammatory bowel disease were searched for relevant studies.

The following search strategy was performed in the respective databases: ("Crohn*[TIAB] OR IBD [TIAB] OR Inflammatory bowel disease*[TIAB] AND JAK [MeSH] OR janus kinase inhibitor[TIAB]) AND (randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized [TIAB] OR placebo [TIAB] OR drug therapy [Subheading] OR randomly [TIAB] OR trial [TIAB] OR groups [TIAB]). Non-English literature was excluded.

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LACK OF EFFICACY OF TOFACITINIB IN CROHN'S DISEASE

As mentioned above Tofacitinib (Pfizer Inc., New York, United States) has shown promising results for the treatment of UC and has been approved by FDA and EMA as well as other regulatory agencies (e.g. SwissMedic) [5,7,53-56]. Tofacitinib is a rather broad JAK inhibitor that besides a main activity for JAK1 and JAK3 also inhibits tyrosine kinases outside the JAK family [2,55]. Therefore, it has always been a matter of discussion whether its action can solely be attributed to JAK inhibition [2]. Tofacitinib has a functional half-life of ~3 h making multiple dosing more promising than single dosing [57-59]. Hepatic metabolism (70%) is more important than renal clearance (30%) for the excretion of the drug [57-59]. This explains why both liver disease and renal insufficiency have to be taken into account when oral dosing is decided.

Tocatinib was tested in CD patients initially in a clinical phase IIa induction of remission design (NCT00615199) [60]. The results presented by Sandborn and coworkers of this 4-week induction study with moderate-to-severe CD were reported in 2014 [60]. 139 CD patients were randomized to either placebo, tofacitinib 1 mg, 5 mg, or 15 mg twice daily (BID). 48 centers in 12 countries contributed to this placebo-controlled, randomized multicenter trial [60]. The primary endpoint in this trial was not clinical remission but clinical response at week 4 (defined as a decrease from baseline in the Crohn's Disease Activity Index (CDAI) score of > 70 points [CR70]). A secondary end point was clinical remission (CDAI <150) at week 4. In contrast to the findings for UC patients disappointingly no differences in clinical response or remission between the placebo group and the treatment groups could be observed. A clinical response was seen in 47% of placebo treated patients, 36% of patients receiving 1 mg tofacitinib BID, 58% in the 5mg BID group and 46% in the 15 mg group [60]. Clinical remission was reported in 21% of placebo treated patients and in 31%, 24% and 14% of the 1-, 5-, and 15-mg groups of tofacitinib treated patients [60]. In the 15-mg dose group reduced levels of CRP and fecal calprotectin as compared to baseline were reported. Placebo response and remission rates in this trial were greater than expected and higher as in comparable studies on anti-TNF

antibodies. The study was criticized because of the short time for induction therapy of only four weeks. This four week end-point was initially chosen to reduce placebo response rates group [60]. In addition, the selected patients had a relatively mild disease course: only 21% of placebo patients previously had received thioguanines and only 2% previously had failed anti-TNF therapy [60]. Furthermore, only 56% of patients had increased fecal calprotectin concentrations (>250 microg/g feces).

Subsequently, tofacitinib for the induction and maintenance of remission and clinical response in patients with CD was further investigated in two placebo-controlled, randomized, multicenter IIb trials (NCT013932626 and NCT01393899) reported by Panes et al. in 2017 [61]. Patients were enrolled into two sequential and integrated phase IIb, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging, multicentre trials for induction (induction study) and maintenance (maintenance study) of remission [61]. The studies were conducted at 80 sites in 18 countries. Adult patients with moderate-to-severe CD (CDAI between 220 and 450) were included. Endoscopic activity had to be confirmed, however, not by central reading. Patients with an inadequate response or intolerance to steroids, thiopurines, methotrexate, or anti-TNF antibodies were eligible. The study design intended a 3:2:2:4 randomization (placebo, 5, 10, or 15mg tofacitinib BID). Treatment duration in the induction-trial was eight weeks. The 15 mg BID treatment group was stopped during the trial and patients finally were randomized 1:1:1 (placebo, 5 or 10mg tofacitinib BID) [61]. If patients had a significant reduction of disease activity (decrease of CDAI of > 100 points) or achieved a clinical remission (as usual defined as CDAI <150) at week 8 they could be re-randomized 1:1:1 to receive either placebo or tofacitinib 5 or 10mg BID for another 26 weeks (maintenance phase). Steroid tapering during the maintenance study was mandatory with a reduction of corticosteroid doses of 5mg prednisolone-equivalent weekly until 20 mg/day, and then by 2.5 mg/week until 10 mg/day.

In the induction study the primary endpoint was clinical remission (as mentioned, CDAI <150 at week 8). Secondary endpoints in the induction study were clinical response with a decrease of the CDAI of either 70 points (CR70) or 100 points (CR100) as compared to baseline CDAI [61]. 280 CD patients were randomized in the induction study (92 placebo treated and 86 either 5mg or 10 mg tofacitinib treated).

There was a high rate of patients pre-exposed to anti-TNF antibodies: 76.9% in the placebo arm and 77.9% treated with tofacitinib [61].

At the end of the treatment phase at week 8 no significant differences between the placebo group and the treatment groups could be observed (figure 1). Clinical remission was reported for 36.7% placebo treated patients, 43.5% of patients treated with 5 mg tofacitinib BID and 43.0% of patients for 10 mg tofacitinib BID [61]. The high rate of patients achieving remission in the placebo arm again was surprising. With respect to secondary endpoint a significantly higher rate of the CR100 (reduction of 100 points in CDAI) was seen with 5 mg tofacitinib BID as compared to placebo (70.6% vs. 54.4%, $p < 0.05$). Similar the reduction of 70 points in CDAI was significantly higher in the 5 mg tofacitinib group as compared to placebo treated CD patients (76.5% vs. 62.2%, $p < 0.05$). However, again the high placebo response rates were surprising and unexpected.

Further, Panes et al. performed a post-hoc analysis: As patient reported outcomes were regarded to be increasingly important by the regulators the investigators analyzed the “patient reported outcome” (PRO) remission: Two PRO scores were evaluated. The PRO2 (calculated as the sum of stool frequency and abdominal pain scores) for which remission is <75, and the PRO3 (calculated as the sum of stool frequency, abdominal pain and general well-being scores) for which remission is defined <80 points [61]. For the PROs Panes et al. found differences between placebo and treatment groups, PRO2: 40.0% versus 58.8%, $p < 0.05$ and PRO3 24.4 versus 38.8%, $p < 0.05$). Furthermore, patients treated with tofacitinib had greater mean decreases in CRP over the course of the study as compared to placebo ($p < 0.001$) [61]. In contrast, there were surprisingly no significant differences for fecal calprotectin between the groups.

For the maintenance study (randomization at week 8 of the inductions study) the primary endpoint was defined as clinical remission (CDAI < 150) or clinical response (CR100) at week 26 [61]. Secondary endpoints were change in CRP and fecal calprotectin. 180 patients could be re-randomized for this maintenance study. 59 patients received placebo, 60 patients were in the 5 mg tofacitinib BID group, and 61 patients were randomized to the 10 mg tofacitinib BID group. Similar to the induction

study the primary endpoint of the maintenance trial was not achieved (figure 2) [61]. There was no significant difference for the patients that were in clinical remission at week 26 and no difference for clinical response (CR100). For the secondary endpoints, significantly lower CRP and fecal calprotectin was observed in the 10 mg tofacitinib group as compared to placebo.

Whereas the primary endpoints of both studies could not be met, a modest effect of tofacitinib was seen for the secondary endpoints of CR70 and CR100 at week 8 [61]. Again the relatively high placebo rates raised doubts regarding the study design. The lack of a requirement for central reading was highlighted, however, it remains questionable whether this had such a high influence. An important aspect certainly is, that there was no protocol defined threshold for an objective marker of disease activity e.g. for CRP or fecal calprotectin levels at baseline.

The further development of tofacitinib in CD was stopped after these trials.

FILGOTINIB HAS DEMONSTRATED EFFICACY IN PHASE II IN CROHN'S DISEASE

Filgotinib (GLPG0634, GS-6034, Galapagos) has a 28-fold selectivity for JAK1 over JAK2 and is subsequently regarded as a JAK1 targeted JAK inhibitor. Filgotinib has a longer half life of ~6 h for the parent compound and ~23 h for the active metabolite as compared to tofacitinib [62]. This allows a once daily dosing.

The efficacy of filgotinib for the induction of remission in moderate to severe CD patients was studied in the randomized, placebo-controlled, multicenter phase II FITZROY study [12]. The inclusion criteria were targeted on adult CD patients with a CDAI between 220 and 450. 52 centers in nine European countries contributed. In contrast to the tofacitinib studies the FITZROY design included a central endoscopy reading. Patients could be included if the central reader agreed that there was an ulceration score of >1 in at least one ileocolonic segment and total SES-CD > 7. Eligible patients were randomized 1:3 to placebo or filgotinib 200mg once daily [12]. Stratification was performed according to anti-TNF antibody exposure, baseline corticosteroid use and baseline CRP. The initial treatment period was 10 weeks [12].

After 10 weeks, patients not responding to placebo were switched to filgotinib 100mg daily for 10 weeks. Responders from the filgotinib group were re-randomized 1:2:2 to receive either placebo or filgotinib 100mg daily or 200mg daily. The complicated study design was completed by an arm for non-responders to filgotinib during the initial 10 weeks. They were randomized 1:3 to receive ether placebo or 200mg filgotinib daily.

The primary endpoint of the FITZROY study was clinical remission (CDAI < 150) at week 10 [12]. Secondary endpoints were clinical response (as measured by CDAI and PRO2), endoscopic response (SES-CD reduction > 50%), endoscopic remission (SES-CD < 4 and ulcerated surface subscore < 1 in all segments), mucosal healing (SES-CD = 0), deep remission (CDAI<150 and SES-CD< 4 and ulcerated surface subscore < 1 in all segments) as well as changes in CRP and fecal calprotectin [12]. Endoscopic readouts were evaluated by central reading. In the FITZROY study 174 patients were randomized. Of them 44 patients received placebo and 130 patients received 200mg filgotinib daily.

The primary endpoint was reached in the FITZROY study (figure 1). Clinical remission was found in 23% of CD patients treated with placebo as compared to 47% of patients that received 200 mg filgotinib daily (p=0.0077) in the intention-to-treat population (Δ 24 %) [12] (figure 1). The difference was higher in anti-TNF naïve patients (13% vs 60%) [12]. With respect to the secondary endpoints a significant difference was seen for CR100 (41% vs 59%, p < 0.05) and PRO2 (30% vs. 50% (P < 0.03) [12]. No significant difference between placebo and filgotinib 200 mg was observed for the following secondary endpoints: SES-CD 50% response (14% vs. 25, p = 0.16), endoscopic remission (7% vs. 14%, p = 0.31), mucosal healing (2% vs 4%, p = 0.82), and deep remission (2% vs 8%, p = 0.31). Especially the low rates for endoscopic remission and mucosal healing were somewhat disappointing. For the second 10 weeks study period 50% (200 mg) and 71% (100 mg) of initial filgotinib responders randomized were in clinical remission at week 20. However, this second study part was not powered for statistical analysis (figure 2).

Despite the relatively disappointing rates for endoscopic endpoints and mucosal healing (only 4% of patients achieved mucosal healing) the overall positive data

stimulated a large phase III induction and maintenance trial evaluating filgotinib in moderate-to-severe CD (Diversity1, NCT02914561). Furthermore, a phase II trial evaluating the efficacy of filgotinib in fistulizing Crohn's disease has been initiated (Divergence2, NCT03077412). In addition, a phase II trial evaluating the efficacy of filgotinib for small bowel CD has been started (NCT03046056).

UPADACITINIB DOES NOT REACH ITS PRIMARY ENDPOINTS IN PHASE II IN CROHN'S DISEASE BUT MEETS SOME SECONDARY ENDPOINTS

Upadacitinib (ABT-494, AbbVie) similar to Filgotinib is an oral JAK1 selective inhibitor with an even higher (74-fold) selectivity for JAK1 over JAK2 [63]. Upadacitinib has a half-life of ~4 h, which is shorter than filgotinib [63]. Similar to tofacitinib upadacitinib is eliminated 80% via hepatic metabolization [CYP3A4 & CYP2D6] and 20% by urinary excretion (20%). Subsequently hepatic and renal functions need to be considered for dosing.

The efficacy of upadacitinib for the induction and maintenance of remission in moderate-to-severe CD patients was studies in a randomized, placebo-controlled multicenter phase II trial (CELEST) which so far is only published in abstract form [64-67].

The study design included a 16-week induction phase and a 36-week blinded extension phase. Similar to the above mentioned trials patients were eligible when they had moderate to severe CD with a CDAI between 220 and 450. Again, the endoscopic activity was evaluated to only include truly inflamed and active CD patients (SES-CD > 6 or > 4 for isolated ileal disease). Patients were randomized to receive either placebo or 3, 6, 12, 24mg BID or 24 mg once upadacitinib [66-68]. The number of patients that had previously received anti-TNF therapy was the highest of all trials reported here: 96% of patients in CELEST were anti-TNF experienced [66-68]. The co-primary endpoints were clinical remission and endoscopic remission (SES-CD < 4 and >2-point reduction from baseline with no subscore >1). Secondary endpoints were modified clinical remission (stool frequency score < 2.8 and abdominal pain score < 1.0) clinical response (defined by a > 30% reduction scores)

and endoscopic response (defined by > 25% reduction in baseline SES-CD). 220 patients were randomized in the CELEST trial of whom 37 received placebo, 39 received 3mg upadacitinib BID, 37 received 6mg upadacitinib BID, 36 received 12 mg upadacitinib BID, 36 received 24 mg upadacitinib BID, and 35 received 24 mg upadacitinib once daily [66-68].

At week 16 clinical remission was not significantly different for the upadacitinib groups as compared to placebo (figure 1). The highest difference was seen for 6 mg upadacitinib BID versus placebo for PRO-defined clinical remission (11% vs 27%, P < 0.10). However, no clear dose response could be observed (figure 1). In subgroup analyses for patients receiving corticosteroids at baseline, clinical remission was significantly more frequent in patients treated with upadacitinib 24 mg BID (0% vs 33.3%, p < 0.05) [65,68,69]. For the secondary endpoint of endoscopic remission a dose response could be found [65,68,69]. Whereas no patients treated with placebo achieved endoscopic remission 14% of CD patients treated with upadacitinib 24 mg daily and 22% of CD patients treated with upadacitinib 24 mg BID were in endoscopic remission at week 16 (p < 0.05 and p < 0.01, respectively). Patients that received either 6mg upadacitinib BID, 12 mg upadacitinib BID, 24 mg upadacitinib BID, or 24 mg upadacitinib daily were more likely to achieve > 25% and >50% reductions in SES-CD as compared to placebo (p < 0.05 for all comparisons) [65,66,69-72].

After the 16-week induction patients were randomized 1:1:1 to receive either 3mg upadacitinib BID, 12 mg upadacitinib BID, or 24 mg upadacitinib once daily for 36 weeks. The protocol was amended to drop the 24 mg once daily dose and instead a 6 mg upadacitinib BID treatment arm was added. 180 patients were re-randomized. A certain dose dependency was observed: In patients that had achieved clinical response by week 16, clinical remission was observed in 25% (3mg BID), 28.6% (6mg BID), 41.4% (12 mg BID), and 31.6% (24 mg once daily) of patients receiving upadacitinib (figure 2). In patients that had achieved clinical AND endoscopic response at week 16, endoscopic remission was observed in 25% (3mg BID), 25% (6mg BID), 37.5% (12 mg BID), and 10% (24 mg once daily) of patients receiving upadacitinib [64]

Based on the findings of the CELEST trial two large phase III trials enrolling patients failing either biologic (NCT03345836) or conventional non-biologic (NCT03345849) therapies have been initiated.

NEW JAK RELATED MOLECULES IN DEVEOPMENT IN CD

Preliminary data suggest that besides the "classical" JAKs TYK2 may be a therapeutic target in CD. No TYK2-selective so far is approved by the agencies. TKY2 is involved in IL-12, IL-13 and IFN signaling. The relative narrow range of cytokines dependent on TYK2 may reduce side effects of inhibition [73].

Therefore, BMS-986165 (Bristol-Myers Squibb) is now studied in IBD clinical trials. BMS-986165 selectively inhibits TYK2 [74,75]. It binds exclusively to the active catalytic site of TYK2 which irreversibly inhibits TYK2 activation [74]. A phase II placebo-controlled, randomized, multicenter, multidosing interventional study (LATTICE) has been initiated to evaluate the safety and efficacy of BMS-986165 for the induction and maintenance of remission in patients with moderate-to-severe CD.

With respect to optimization of efficacy PF-06700841 and PF-06651600 (Pfizer) are currently studied in IBD. JAK2 forms a homodimer important for erythropoietin signaling. To avoid JAK2 inhibition mediated side effects, dual JAK1/TYK2 inhibition without influence on JAK2 signaling could be interesting. PF-06700841 is a new selective JAK inhibitor also mainly targeting TYK2 but also JAK1 [76,77].

In contrast, PF-06651600 is a selective JAK3 inhibitor [78,79]. In vitro, PF-06651600 was shown to inhibit Th1 and Th17 cell differentiation. PF-06700841 and PF-06651600, are currently under study in phase II in patients with moderate-to-severe CD.

Another approach to avoid side effects of JAK inhibitors is a non-systemic but local application. TD-1473 (Theravance Biopharma) is pan-JAK inhibitor (inhibiting JAK1, JAK2, JAK3 and TYK2) with high affinity. However, it is not absorbed and thus distributes only in the intestinal tract, reducing systemic exposure [80,81]. It is

subsequently regarded to have a gut selective action. In a phase I trial in patients with UC the safety, tolerability and pharmacodynamics of TD-1473 were evaluated [82,83]. TD-1473 was well tolerated over 4 weeks, without serious or opportunistic infections. Low plasma levels and higher colonic tissue concentrations confirmed gut selectivity. Phase II and phase III trials have been initiated to study the efficacy of TD-1473 for the induction and maintenance of remission in patients with moderate to severe CD.

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SAFETY PROFILE OF JAK INHIBITION IN CD PATIENTS

JAK inhibitors have shown a pattern of safety signals in different patient groups. An about 4-fold increased risk for herpes zoster was reported for tofacitinib in patients with rheumatoid arthritis or UC. Furthermore, FDA and EMEA warning with respect to thromboembolic complications were released for tofacitinib in 2019. Patients with thromboembolic risk factors such as hormonal contraceptives should not receive the 10 mg BID dosage according to the EMEA warning.

In the CD induction studies with tofacitinib adverse events (AEs) were reported for 60.4%, 58.1%, and 60.5% of patients receiving placebo, or tofacitinib 5mg and 10 mg BID. In the maintenance study with tofacitinib, AEs were reported in 74.6%, 83.3%, and 78.7% of patients, receiving placebo, or tofacitinib 5mg and 10 mg BID [60,61]. Serious adverse events (SAEs) were more frequently reported in the maintenance study mainly in patients receiving 10 mg tofacitinib BID (11.6% in induction, 13.1% in maintenance) as compared to 5 mg BID (3.5% in induction, 10.0% in maintenance) or placebo (3.3% in induction, 11.9% in maintenance) [61]. In the maintenance study, three patients in the tofacitinib 5mg BID group reported serious infections and two patients in the tofacitinib 10 mg BID group. No cases of opportunistic infections (OI) were reported. Similar to other studies two cases of herpes zoster were reported the tofacitinib 10 mg BID group. No thromboembolic complications were reported in the CD trials.

For the FITZROY study in the pooled safety analysis of both parts AEs were not significantly different between the placebo group and the filgotinib groups (67% versus 75%) [12]. SAEs were also not statistically more frequent in the filgotinib groups albeit there was a numerical difference (4% for placebo, 9% for filgotinib). This is relevant, as serious infections were only reported in filgotinib treated patients (4/152) [12]. Again, there was a signal for herpes zoster, making a group effect for JAK inhibitor likely.

In the CELEST study for upadacitinib the occurrence of AEs was not significantly different between the placebo group (73%) and the upadacitinib arms (82%) [67,68]. In contrast, SAEs occurred in 5% of patients in the placebo group whereas 15% of

patients in the upadacitinib arms had SAEs [67,68]. Serious infections occurred in eight patients on upadacitinib. Among them were four cases of sepsis. Furthermore, two patients on upadacitinib had a myocardial infarction and two patients suffered from small bowel perforations [67,68].

As mentioned EMA recently recommended that tofacitinib 10mg BID should not be given to patients with thromboembolic risk factors such as current use of oral contraceptive or hormonal therapy, decompensated heart disease, history of previous thromboembolic events, hereditary coagulopathy, cancer and patients with recent major surgical interventions [84]. Pulmonary embolisms also occurred in the UC developments program for tofacitinib [84].

DISCUSSION

JAK inhibitors represent an interesting class of molecules. A number of compounds have been approved for a variety of hematological and auto-immune diseases. The development of JAK inhibitors in the field of IBD has also shown progress over the last years.

Whereas data in UC are promising and have led to the approval of tofacitinib, treatment results in CD are in general less impressive so far. The study design of the tofacitinib studies has been criticized and the high placebo rate found in the tofacitinib trials in CD patients certainly raises concerns. However, endoscopic endpoints in the FITZROY or CELEST studies also show no groundbreaking effect albeit treatment periods in the trials have been short (8-10 weeks).

Nevertheless, JAK inhibitors are an attractive therapeutic option also in CD patients as their oral bioavailability is high. The safety profile certainly needs to be investigated in more details. The occurrence of thromboembolic complications, herpes zoster and serious infections raises concerns. Risk/benefit analyses should be performed for this class of compounds in CD. An appealing approach certainly are more specific (e.g. TYK2 inhibition) or gut selective compounds that are under development.

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Figure 1: Induction of clinical remission

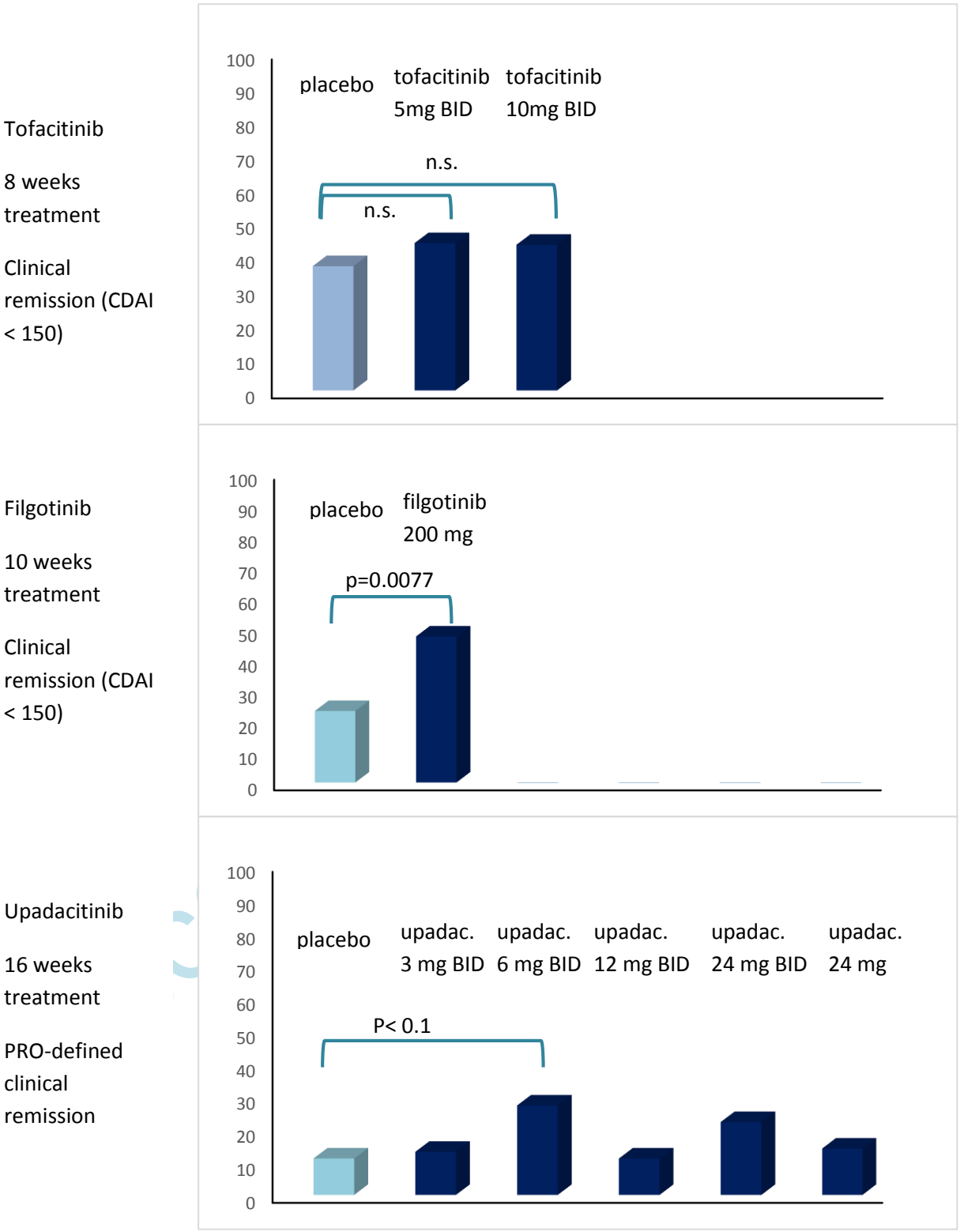

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Figure 2: Maintenance of remission